

**CHLORAMPHENICOL SODIUM SUCCINATE - chloramphenicol sodium succinate injection, powder, lyophilized, for solution**  
**General Injectables and Vaccines, Inc**

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**Chloramphenicol Sodium Succinate 1 gm Injection, USP 1 gm Vial**

**Boxed Warning**

**WARNING**

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the INDICATIONS AND USAGE section. It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.

**Description**

**IMPORTANT CONSIDERATIONS IN PRESCRIBING INJECTABLE CHLORAMPHENICOL SODIUM SUCCINATE.**

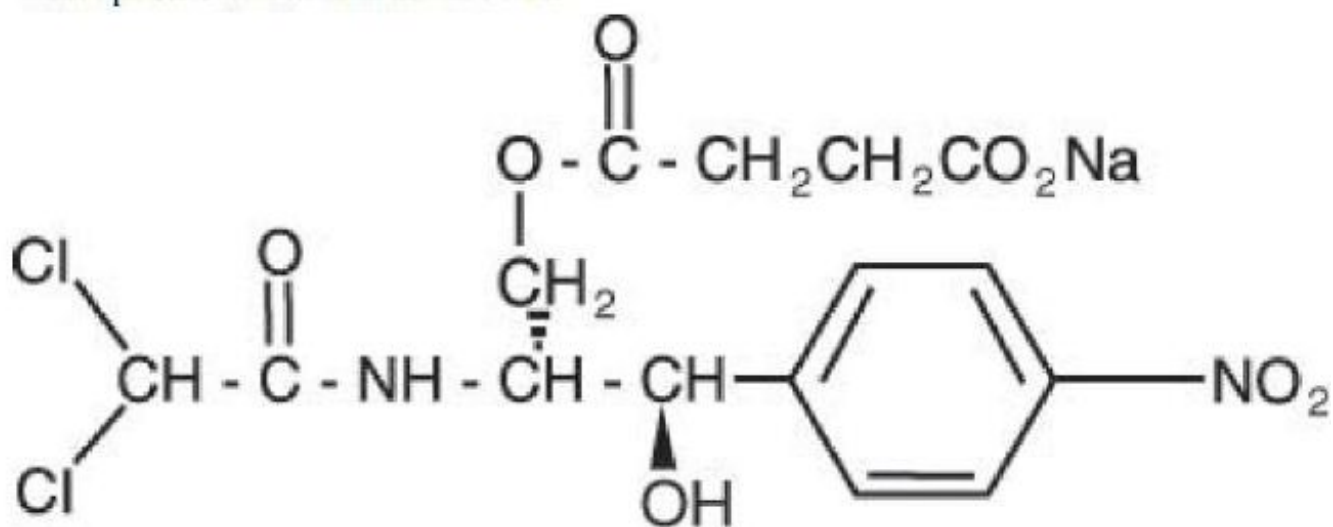
**CHLORAMPHENICOL SODIUM SUCCINATE IS INTENDED FOR INTRAVENOUS USE ONLY. IT HAS BEEN**

**DEMONSTRATED TO BE INEFFECTIVE WHEN GIVEN INTRAMUSCULARLY.**

1. Chloramphenicol sodium succinate for injection must be hydrolyzed to its microbiologically active form, and there is a lag in achieving adequate blood levels compared with the base given intravenously.
2. The oral form of chloramphenicol is readily absorbed and adequate blood levels are achieved and maintained on the recommended dosage.
3. Patients started on intravenous chloramphenicol sodium succinate for injection should be changed to the oral form as soon as practicable.

Chloramphenicol is an antibiotic that is clinically useful for, and should be reserved for, serious infections caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. Sensitivity testing is essential to determine its indicated use, but may be performed concurrently with therapy initiated on clinical impression that one of the indicated conditions exists (see INDICATIONS AND USAGE section). When reconstituted as directed, each vial contains a sterile solution equivalent to 100 mg of chloramphenicol per mL (1g/10mL). Each gram (10 mL of a 10% solution) of chloramphenicol sodium succinate contains approximately 52 mg (2.25 mEq) of sodium. The chemical name for chloramphenicol sodium succinate is D-threo-(-)-2, 2-Dichloro-N-[b- hydroxy-a-(hydroxymethyl)-p-nitrophenethyl] acetamide a-(sodium succinate).

The empirical and structural formulas are:



### Clinical Pharmacology

In vitro chloramphenicol exerts mainly a bacteriostatic effect on a wide range of gram-negative and gram-positive bacteria and is active in vitro against rickettsias, the lymphogranuloma-psittacosis group and *Vibrio cholerae*. It is particularly active against *Salmonella typhi* and *Hemophilus influenzae*. The mode of action is through interference or inhibition of protein synthesis in intact cells and in cell-free systems.

Chloramphenicol administered orally is absorbed rapidly from the intestinal tract. In controlled studies in adult volunteers using the recommended dosage of 50 mg/kg/day, a dosage of 1 g every 6 hours for 8 doses was given. Using the microbiological assay method, the average peak serum level was 11.2 mcg/mL one hour after the first dose. A cumulative effect gave a peak rise to 18.4 mcg/mL after the fifth dose of 1 g. Mean serum levels ranged from 8 to 14 mcg/mL over the 48-hour period. Total urinary excretion of chloramphenicol in these studies ranged from a low of 68% to a high of 99% over a three-day period. From 8% to 12% of the antibiotic excreted is in the form of free chloramphenicol; the remainder consists of microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most chloramphenicol detected in the blood is in the microbiologically active free form. Despite the small proportion of unchanged drug excreted in the urine, the concentration of free chloramphenicol is relatively high, amounting to several hundred mcg/mL in patients receiving divided doses of 50 mg/kg/day. Small amounts of active drug are found in bile and feces. Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood. Measurable levels are also detected in pleural and in ascitic fluids, saliva, milk, and in the aqueous and vitreous humors. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of neonates than in maternal blood.

### Indications and Usage

**In accord with the concepts in the Warning Box and this INDICATIONS AND USAGE section, chloramphenicol must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated. However, chloramphenicol may be chosen to initiate antibiotic therapy on the clinical impression that one of the conditions below is believed to be present; in vitro sensitivity tests should be performed concurrently so that the drug may be discontinued as soon**

**as possible if less potentially dangerous agents are indicated by such tests. The decision to continue use of chloramphenicol rather than another antibiotic when both are suggested by in**

**vitro studies to be effective against a specific pathogen should be based upon severity of the infection, susceptibility of the pathogen to the various antimicrobial drugs, efficacy of the various drugs in the infection, and the important additional concepts contained in the Warning Box above.**

**1. Acute infections caused by *Salmonella typhi*\***

It is not recommended for the routine treatment of the typhoid carrier state.

**2. Serious infections caused by susceptible strains in accordance with the concepts expressed above:**

- a) *Salmonella* species
- b) *H. influenzae*, specially meningeal infections
- c) *Rickettsia*
- d) Lymphogranuloma-psittacosis group
- e) Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections
- f) Other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents.

**3. Cystic fibrosis regimens**

\*In treatment of typhoid fever some authorities recommend that chloramphenicol be administered at therapeutic levels for 8 to 10 days after the patient has become afebrile to lessen the possibility of relapse.

**Contraindications**

Chloramphenicol is contraindicated in individuals with a history of previous hypersensitivity and/or toxic reaction to it. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.*

**Precautions**

Baseline blood studies should be followed by periodic blood studies approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia or any other blood study findings attributable to chloramphenicol. However, it should be noted that such studies do not exclude the possible later appearance of the irreversible type of bone marrow depression.

Repeated courses of chloramphenicol treatment should be avoided if at all possible. Treatment should not be continued longer than required to produce a cure with little or no risk or relapse of the disease.

Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.

Excessive blood levels may result from administration of the recommended dose to patients with impaired liver or kidney function, including that due to immature metabolic processes in the infant. The dosage should be adjusted accordingly, or preferably, the blood concentration should be determined at appropriate intervals.

There are no studies to establish the safety of this drug in pregnancy.

Since chloramphenicol readily crosses the placental barrier, caution in use of the drug is particularly important during pregnancy at term or during labor because of the potential toxic effects on the fetus (gray syndrome).

Precaution should be used in therapy of premature and full-term infants to avoid "gray syndrome" toxicity (see ADVERSE REACTIONS). Serum drug levels should be carefully followed during therapy of the newborn infant.

Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant.

the use of this antibiotic, as with other antibiotics, may result in an overgrowth of non-susceptible organisms, including fungi. If infections caused by non-susceptible organisms appear during therapy, appropriate measures should be taken.

## **Adverse Reactions**

### **1. Blood Dyscrasias**

The most serious adverse effect of chloramphenicol is bone marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. An irreversible type of marrow depression leading to aplastic anemia with a high rate of mortality is characterized by the appearance weeks or months after therapy of bone marrow aplastic or hypoplasia. Peripherally, pancytopenia is most often observed, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may be depressed. A reversible type of bone marrow depression, which is dose related, may occur. This type of marrow depression is characterized by vacuolization of the erythroid cells, reduction of reticulocytes and leukopenia, and responds promptly to the withdrawal of chloramphenicol.

An exact determination of the risk of serious and fatal blood dyscrasias is not possible because of lack of accurate information regarding 1) the size of the population at risk, 2) the total number of drug-associated dyscrasias, and 3) the total number of non-drug associated dyscrasias.

In a report to the California State Assembly by the California Medical Association and the State Department of Public Health in January 1967, the risk of fatal aplastic anemia was estimated at 1:24,200 to 1:40,500 based on two dosage levels.

There have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia.

Paroxysmal nocturnal hemoglobinuria has been reported.

### **2. Gastrointestinal Reactions**

Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

### **3. Neurotoxic Reactions**

Headache, mild depression, mental confusion, and delirium have been described in patients receiving chloramphenicol. Optic and peripheral neuritis have been reported, usually following long-term therapy. If this occurs, the drug should be promptly withdrawn.

### **4. Hypersensitivity Reactions**

Fever, macular and vesicular rashes, angioedema, urticaria, and anaphylaxis may occur. Herxheimer's reactions have occurred during therapy for typhoid fever.

### **5. "Gray Syndrome"**

Toxic reactions including fatalities have occurred in the premature and neonate; the signs and symptoms associated with these reactions have been referred to as the "gray syndrome." One case of gray syndrome has been reported in a neonate born to a mother having received chloramphenicol during labor. One case has been reported in a 3-month-old infant. The following summarizes the clinical and laboratory studies that have been made on these patients:

- a) In most cases therapy with chloramphenicol had been instituted within the first 48 hours of life.
- b) Symptoms first appeared after 3 to 4 days of continued treatment with high doses of chloramphenicol.
- c) The symptoms appeared in the following order:
  - (1) abdominal distension with or without emesis;
  - (2) progressive pallid cyanosis;
  - (3) vasomotor collapse, frequently accompanied by irregular respiration;

- (4) death within a few hours of onset of these symptoms.
- d) The progression of symptoms from onset to exitus was accelerated with higher dose schedules.
- e) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol (over 90 mcg/mL after repeated doses).
- f) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

## **Dosage and Administration**

Chloramphenicol, like other potent drugs, should be prescribed at recommended doses known to have therapeutic activity. Administration of 50 mg/kg/day in divided doses will produce blood levels of the magnitude to which the majority of susceptible microorganisms will respond.

**As soon as feasible an oral dosage form of another appropriate antibiotic should be substituted for intravenous chloramphenicol sodium succinate.**

The following method of administration is recommended:

Intravenously as a 10% (100 mg/mL) solution to be injected over at least a one-minute interval. This is prepared by the addition of 10 mL of an aqueous diluent such as water for injection or 5% dextrose injection.

### **Adults**

Adults should receive 50 mg/kg/day in divided doses at 6-hour intervals. In exceptional cases patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg/kg/day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible. Adults with impairment of hepatic or renal function or both may have reduced ability to metabolize and excrete the drug. In instances of impaired metabolic processes, dosages should be adjusted accordingly. (See discussion under Newborn Infants.) Precise control of concentration of the drug in the blood should be carefully followed in patients with impaired metabolic processes by the available microtechniques (information available on request).

### **Children**

Dosage of 50 mg/kg/day divided into 4 doses at 6-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (eg, bacteremia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg/kg/day; however, it is recommended that dosage be reduced to 50 mg/kg/day as soon as possible. Children with impaired liver or kidney function may retain excessive amounts of the drug.

### **Newborn Infants**

(See section titled "Gray Syndrome" under ADVERSE REACTIONS.)

A total of 25 mg/kg/day in 4 equal doses at 6-hour intervals usually produces and maintains concentrations in blood and tissues adequate to control most infections for which the drug is indicated. Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. After the first two weeks of life, full-term neonates ordinarily may receive up to a total of 50 mg/kg/day equally divided into 4 doses at 6-hour intervals. These dosage recommendations are extremely important because blood concentration in all premature and full-term neonates under two weeks of age differs from that of other infants neonates. This difference is due to variations in the maturity of the metabolic functions of the liver and the kidneys. When these functions are immature (or seriously impaired in adults), high concentrations of the drug are found which tend to increase with succeeding doses.

### **Infants and Children with Immature Metabolic Processes**

In young infants and other pediatric patients in whom immature metabolic functions are suspected, a dose of 25 mg/kg/day will usually produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by microtechniques. (Information available on request.)

## How Supplied

Chloromycetin Sodium Succinate for Injection, USP is freeze-dried in the vial. When reconstituted as directed, each vial contains a sterile solution equivalent to 100 mg of chloramphenicol per mL (1 g/10 mL).

Product No.	NDC No.	
1115	63323-011-15	Available in packages of 10 vials.

Store between 20° and 25°C (68° and 77°F). [See USP Controlled room Temperature].

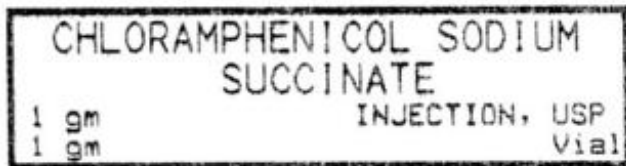
Preservative Free.

APP Pharmaceuticals, LLC  
Schaumburg, IL 60173

## Sample Outer Label

NDC # 52584-011-15  
LOT # XXXX  
Exp: mm-yy  
Serial # XXXXXX

PACKAGED BY GIV  
BASTIAN, VA 24314



SEE MANUFACTURER'S INSERT  
FOR COMPLETE PRODUCT AND  
PRESCRIBING INFORMATION

Keep out of  
children's reach.

Store at controlled room  
temperature 68F to 77F.

SEE ENCLOSED WARNINGS & PRECAUTIONS  
FOR IV USE ONLY  
SOLUTION SHOULD BE USED WITHIN 30 DAYS  
A CLOUDY SOLUTION SHOULD NOT BE USED  
PRESERVATIVE FREE

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### MANUFACTURER INFORMATION

APP Pharmaceuticals Inc

ORIG MFG LOT: XX-XXX-XX



63323-011-15



Item # 2589108

RX ONLY

**CHLORAMPHENICOL SODIUM SUCCINATE**

chloramphenicol sodium succinate injection, powder, lyophilized, for solution

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:52584-011(NDC:63323-011)
<b>Route of Administration</b>	INTRAVENOUS	<b>DEA Schedule</b>	

### Active Ingredient/Active Moiety

<b>Ingredient Name</b>	<b>Basis of Strength</b>	<b>Strength</b>
<b>Chloramphenicol Sodium Succinate</b> (UNII: 872109HX6B) (Chloramphenicol - UNII:66974FR9Q1)	Chloramphenicol Sodium Succinate	133.27 mg in 133.27 mg

### Packaging

#	<b>Item Code</b>	<b>Package Description</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
1	NDC:52584-011-15	1 in 1 BAG		
1		133.27 mg in 1 VIAL		

### Marketing Information

<b>Marketing Category</b>	<b>Application Number or Monograph Citation</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
ANDA	ANDA062365	09/01/2010	

**Labeler** - General Injectables and Vaccines, Inc (108250663)

Revised: 9/2010

General Injectables and Vaccines, Inc